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Neurochemical and Neuroendocrine Effects of Ibogaine in Rats: Comparison to MK-801

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ABSTRACT: Ibogaine (IBO) is a naturally-occurring indole compound that is being evaluated as a potential medication for substance use disorders. Although the precise mechanism of IBO action is unclear, recent *in vitro* data show this drug displays properties similar to the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist MK-801. The purpose of the present work was to compare *in vivo* neurobiological effects of IBO and MK-801 in rats. Groups of male rats ($n = 6-8/\text{group}$) were decapitated 30 and 60 min after receiving intraperitoneal (i.p.) IBO (10 & 100 mg/kg), MK-801 (0.1 & 1.0 mg/kg) or vehicle. Trunk blood was collected for the analysis of plasma prolactin and corticosterone; brains were harvested and dissected for determination of dopamine (DA), serotonin (5-HT) and their metabolites. Both IBO and MK-801 increased corticosterone secretion, but only IBO elevated plasma prolactin. IBO produced dramatic reductions in tissue DA levels with concurrent increases in the metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). This profile of IBO-induced changes in DA transmission was observed in the striatum, olfactory tubercle, and hypothalamus. The effects of MK-801 on DA metabolism did not mimic IBO, as MK-801 tended to increase DA and its metabolites. Neither drug appreciably affected 5-HT systems. Our results suggest that the effects of IBO on neuroendocrine function and DA transmission are not due to MK-801-like properties of IBO. Thus, the *in vivo* mechanism of IBO action cannot be explained simply on the basis of antagonism at NMDA receptors.

INTRODUCTION

Ibogaine (IBO) is an indole alkaloid extracted from the African shrub *Tabernanthe iboga*. The psychoactive properties of IBO have been known for decades,¹ and the drug has recently gained attention as a possible medication for substance use disorders (reviewed by Popik *et al.*²). Evidence for the 'antiaddictive' effects of IBO comes from both preclinical and human studies. In rats, for example, IBO pretreatment decreases the self-administration of cocaine and morphine.³⁻⁵ The drug also alleviates symptoms of naloxone-precipitated withdrawal in morphine-dependent rodents^{6,7} (although see Ref. 8). In a recent clinical study, Sheppard⁹ found that a single IBO treatment completely prevented the appearance of withdrawal symptoms in opiate addicts. Taken together, these promising findings support the utility of IBO as a treatment for drug addiction.

On the other hand, IBO is known to produce adverse effects in rats. Acute injection

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of IBO at doses >10 mg/kg, intraperitoneally (i.p.), elicits behavioral disturbances such as tremors and axataxia.^{6,10} Administration of higher doses of IBO, *i.e.*, 100 mg/kg, i.p., results in Purkinje cell degeneration and reactive gliosis in the cerebellar vermis.^{11,12} More recent investigations show that IBO-induced neuronal damage can occur in many brain areas in addition to the cerebellum.¹³ It is noteworthy that doses of IBO causing neurodegeneration are very close to the doses that decrease morphine and cocaine self-administration (*i.e.*, 40 mg/kg, i.p.). Thus, the development of IBO as a pharmacotherapy should proceed with caution.

Despite extensive research, the mechanisms underlying the antiaddictive and neurotoxic effects of IBO are unknown. It is well established that IBO binds with low μM potency to multiple neuronal targets including sigma-2 receptors, serotonin (5-HT) and dopamine (DA) transporters, *N*-methyl-D-aspartate (NMDA) ion channels, and kappa opioid receptors (summarized in TABLE 1). However, the role of these binding sites in mediating specific actions of IBO has not been resolved. Biodistribution studies in rats show that brain levels of IBO range from 10–20 μM when measured 1 hr after acute administration of 50 mg/kg, per os (p.o., orally),¹⁴ or 40 mg/kg, i.p.¹⁵ These data suggest that the interaction of IBO with μM -affinity binding sites is functionally relevant *in vivo*.

Some investigators have speculated that the antiaddictive properties of IBO might involve antagonist activity at NMDA-coupled ion channels, similar to the effects of MK-801.^{7,16,17} This hypothesis has important implications, since MK-801 is reported to block long-term detrimental effects produced by chronic opioids, ethanol, and psychomotor stimulants.^{18–20} As shown in TABLE 1, IBO inhibits [³H]MK-801 binding in brain membranes.^{21,22} Like MK-801, IBO blocks depolarizations evoked by NMDA in cultured hippocampal neurons and in intact motoneurons.^{7,16,17} Studies in mice show that IBO cross-generalizes to MK-801 as a discriminative stimulus and antagonizes NMDA-induced lethality.^{7,16} Thus IBO exhibits MK-801-like properties in a variety of assay systems.

With respect to the preceding discussion, it seems pertinent to further evaluate the

TABLE 1. Ibogaine (IBO) Inhibits Radioligand Binding to Multiple Sites in Nervous Tissue with Low μM Affinity

Binding Site	K_i (μM)	Citation
Sigma 2 binding sites	0.20–0.25	Mach <i>et al.</i> ⁴²
[³ H]DTG		Bowen <i>et al.</i> ⁴³
5-HT transporters	0.40–0.55	Mash <i>et al.</i> ³⁷
[¹²⁵ I]RTI-55		Staley <i>et al.</i> ¹⁴
DA transporters	1.5–4.0	Sershen <i>et al.</i> ³³
[³ H]WIN-35,248 or		Sweetnam <i>et al.</i> ²²
[¹²⁵ I]RTI-121		Mash <i>et al.</i> ³⁷
NMDA ion channels	1.0–5.6	Popik <i>et al.</i> ²¹
[³ H]MK-801		Staley <i>et al.</i> ¹⁴
		Sweetnam <i>et al.</i> ²²
Kappa opioid receptors	2.1–16.0	Deecher <i>et al.</i> ³⁶
[³ H]U69,593		Sweetnam <i>et al.</i> ²²
Sodium ion channels	8.1–9.0	Deecher <i>et al.</i> ³⁶
Site 2		Sweetnam <i>et al.</i> ²²
[³ H]BTX-B		

Note: The binding site, radiolabeled ligand, and approximate inhibition constant (K_i (μM)) are shown based on the cited references.

NMDA antagonist properties of IBO. In the present work, we compared the acute effects of IBO and MK-801 on indices of DA neurotransmission and stress axis activation. Postmortem tissue levels of DA and its metabolites were determined in dissected brain regions, whereas the stress hormones, prolactin and corticosterone, were measured in plasma. The actions of IBO and MK-801 on these particular neurobiological endpoints were examined for several reasons. First, the essential role of mesolimbic DA neurons in mediating the addictive properties of abused drugs is well accepted.^{23,24} Second, stress hormones, particularly hormones of the hypothalamic-pituitary-adrenal (HPA) axis, are known to modulate the acute and long-term effects of abuse drugs.^{25,26} It seems feasible, therefore, that the antiaddictive effects of IBO might involve changes in DA function and/or activity of the HPA axis. Finally, the effects of IBO on these systems have recently been characterized, and this provides a convenient starting point for comparison to MK-801.^{27,28}

MATERIALS AND METHODS

Animals

Adult male Sprague-Dawley cesarean delivered (CD) rats (250–350 g) from the National Center for Toxicological Research (NCTR) breeding colony were used in these studies. Animals were housed 2 per cage under controlled conditions (lights on: 0600–1800 hr) with free access to food and water. The housing facilities were fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and experiments were carried out in accordance with Institutional Animal Care and Use Committee of the NCTR.

Experimental Procedures

In the first experiment, we evaluated the time-course of IBO effects on DA metabolism and the secretion of stress hormones. Groups of 4–8 rats received i.p. saline or IBO (50 mg/kg) and were sacrificed by decapitation at 15, 30, 60, and 120 min thereafter. An uninjected control group of 6 rats (time zero) was sacrificed in the same experiment. The striatum and frontal cortex were dissected, and trunk blood was collected. The dose of IBO selected was comparable to the dose reported to decrease cocaine and morphine self-administration in rats.^{4,5} Brain tissue and plasma samples were stored at -70°C until the time of assay.

In a second experiment, we compared the effects of IBO and MK-801 on DA metabolism and circulating stress hormones. Groups of 6–8 rats received i.p. saline, IBO (10 and 100 mg/kg), or MK-801 (0.1 and 1.0 mg/kg) and were decapitated 30 min later. The striatum, frontal cortex, and hypothalamus were dissected, and trunk blood was collected. The two doses of IBO selected represent 1) a low behaviorally-active dose,²⁹ and 2) a high neurotoxic dose.^{11,12} The MK-801 doses were matched for comparison based on *in vitro* potency estimates and *in vivo* behavioral effects.^{7,16,30} Brain tissue and plasma samples were stored at -70°C until the time of assay.

Neurotransmitter Determinations

Postmortem tissue levels of DA and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were determined by high-pressure liquid chro-

matography coupled to electrochemical detection (HPLC-EC) as described by Ali and co-workers.^{27,31} Briefly, brain tissue was weighed and a measured volume (20% w/v) of 0.2 N perchloric acid containing 100 ng/mg of the internal standard, 3,4-dihydroxybenzylamine (DHBA), was added. The tissue was disrupted by ultrasonication, centrifuged (15,000 rpm for 7 min), and 150 μ l of the supernatant was filtered. Aliquots of 25 μ l were injected onto the HPLC-EC system for the separation of DA and its metabolites.

The analytical system included a Waters Model 510 HPLC pump (Milford, MA), a Rheodyne Model 7125 injector (Cotati, CA), a Supelco C-18 3- μ m reversed-phase analytical column (Bellefonte, PA), and a Bioanalytical Systems LC-4B amperometric detector (W. LaFayette, IN) equipped with a glassy carbon working electrode set at +750 mV relative to a Ag/AgCl reference. The mobile phase consisted of 0.07 M potassium phosphate, pH 3.0, 8% methanol and 1.02 mM 1-heptane sulfonic acid. Chromatograms were recorded and integrated on a Perkin-Elmer LCI-100 integrator (Norwalk, CT). The levels of DA, DOPAC, and HVA were calculated by comparing peak heights of unknowns to peak heights of standards.

Plasma Hormone Determinations

Plasma prolactin and corticosterone concentrations were determined by double-antibody radioimmunoassay (RIA). Prolactin was assayed using materials generously provided by the National Hormone and Pituitary Program (Baltimore, MD) Anti-serum directed against rat prolactin, rPRL-S-9, was diluted 1:12,500, and rPRL-RP-3 served as the reference standard. [¹²⁵I]Prolactin was obtained from Hazleton Laboratories (Vienna, VA). Plasma samples (50 μ l) were analyzed in duplicate within a single assay, and the intraassay coefficient of variability was 6.5%. Corticosterone was assayed using commercially available kits (ICN Biomedicals, Irvine, CA). Plasma samples (10 μ l) were analyzed in duplicate within a single assay, and the average intraassay coefficient of variability was 7.5%.

Statistical Analysis

All neurochemical and hormone data were evaluated using analysis of variance (ANOVA) followed by Duncan's multiple range test for post hoc comparisons. A value of $p < 0.05$ was considered the minimum criterion for statistical significance.

RESULTS

IBO Time-Course Evaluation

The time-course effects of IBO on DA metabolism in the cortex and striatum are shown in FIGURE 1, panels A and B. Saline injection did not alter the concentrations of DA or its metabolites at any time point when compared to uninjected rats. Therefore, neurochemical data from saline-treated rats were pooled for the $t = 0$ control group ($n = 20$). After IBO injection, DA levels were decreased in cortex ($F_{4,40} = 3.85$, $p < 0.01$) and striatum ($F_{4,40} = 25.09$, $p < 0.0001$). Post hoc analysis revealed that this reduction in DA was significant after 30 min in cortex and at 30, 60 and 120 min in striatum. IBO produced time-dependent increases in DOPAC levels in the cortex ($F_{4,40} = 7.32$, $p < 0.0001$) and striatum ($F_{4,40} = 8.09$, $p < 0.0001$); DOPAC was significantly ele-

vated at 15 and 60 min in cortex and at 15, 30 and 120 min in striatum. HVA was increased by IBO in the cortex ($F_{4,40} = 35.67$, $p < 0.0001$) and striatum ($F_{4,40} = 10.71$, $p < 0.0001$). In general, augmented HVA levels paralleled DOPAC levels in both regions.

FIGURE 2 depicts the effects of acute saline or IBO administration on plasma prolactin (panel A) and corticosterone (panel B). Saline injection elevated prolactin ($F_{4,18} = 2.96$, $p < 0.05$) and corticosterone ($F_{4,18} = 9.69$, $p < 0.001$) compared to preinjection levels. This effect was transient, reaching statistical significance at 15 min for prolactin, and at 15 and 30 min for corticosterone. IBO increased circulating prolactin ($F_{1,35} = 14.79$,

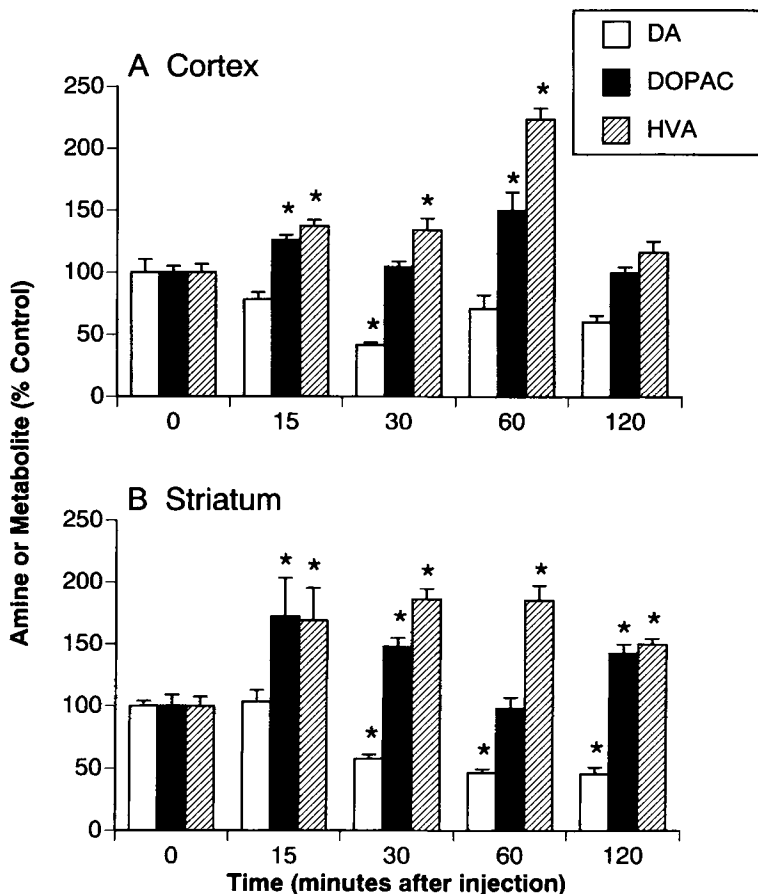


FIGURE 1. Effect of i.p. saline (1 ml/kg) or IBO (50 mg/kg) on DA, DOPAC and HVA concentrations in the (A) frontal cortex and (B) striatum of male rats. Groups of rats ($n = 4-8$ rats/group) were sacrificed immediately before and at 15, 30, 60, and 120 min after IBO treatment. Values are expressed as % control of the data pooled from saline-treated rats at all time points ($n = 20$). Control levels of DA, DOPAC and HVA in the frontal cortex were 40.6 ± 2.2 , 18.5 ± 2.4 and 17.3 ± 1.5 ng/g tissue, respectively. Control levels of DA, DOPAC and HVA in the striatum were 1216.1 ± 50.1 , 153.8 ± 13.9 and 78.0 ± 5.8 ng/g tissue, respectively. * $p < 0.05$ with respect to time zero control (Duncan's test).

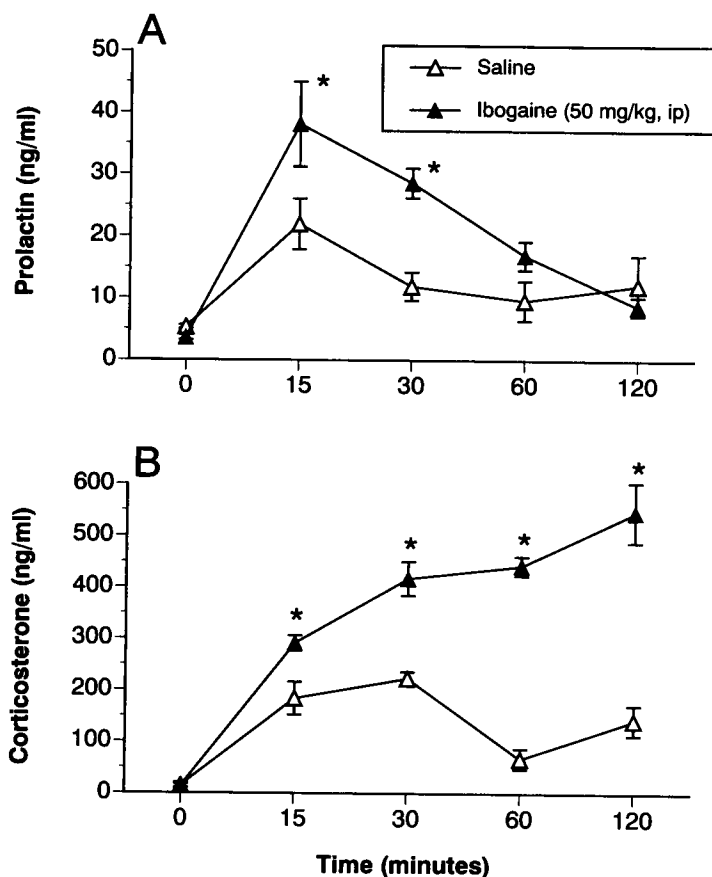


FIGURE 2. Effect of i.p. saline (1 ml/kg) or IBO (50 mg/kg) on plasma levels of (A) prolactin and (B) corticosterone in male rats. Trunk blood was obtained immediately before and at 15, 30, 60 and 120 min after injection. Data represent means $\pm$ SEM of $n = 4-8$ rats/group. * $p < 0.05$ compared to saline-treated group.

$p < 0.005$) and corticosterone ($F_{1,35} = 74.95$, $p < 0.0001$) relative to saline-injected controls. Post hoc analysis revealed that the IBO-induced prolactin increase was significant at 15 and 30 min postinjection, whereas the stimulation of corticosterone secretion was more prolonged, reaching statistical significance at 15, 30, 60 and 120 min.

IBO Versus MK-801 Comparison

The effects of IBO on DA metabolism in the cortex, striatum and hypothalamus are shown in FIGURE 3, panels A, B, and C, respectively. IBO decreased DA in all three brain regions: cortex ($F_{2,17} = 4.51$, $p < 0.05$), striatum ($F_{2,17} = 42.50$, $p < 0.0001$), and hypothalamus ($F_{2,17} = 11.46$, $p < 0.001$). Post hoc tests revealed this reduction in DA was

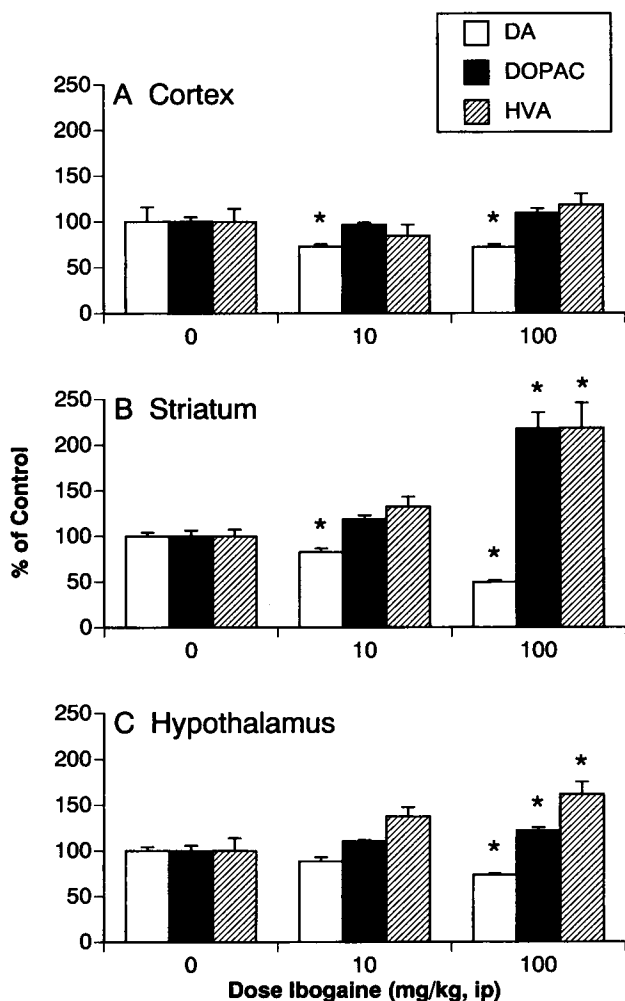


FIGURE 3. Effect of i.p. saline or IBO (10 & 100 mg/kg) on DA, DOPAC and HVA concentrations in the (A) frontal cortex, (B) striatum and (C) hypothalamus of male rats. Groups of rats ($n = 6-8$ rats/group) were sacrificed 30 min after IBO treatment. Values are expressed as % control of the data from saline-treated rats. Control levels of DA, DOPAC and HVA in the frontal cortex were 50.9 ± 6.2 , 25.7 ± 3.4 , and 11.4 ± 1.5 ng/g tissue, respectively. Control levels of DA, DOPAC and HVA in the striatum were 1290.1 ± 68.6 , 139.9 ± 8.8 , and 79.1 ± 5.8 ng/g tissue, respectively. Control levels of DA, DOPAC and HVA in the hypothalamus were 60.6 ± 3.1 , 24.2 ± 1.4 , and 8.2 ± 1.4 ng/g tissue, respectively. * $p < 0.05$ with respect to time zero control.

significant at the 10-mg/kg and 100-mg/kg doses in the cortex and striatum, but only at the 100-mg/kg dose in the hypothalamus. The levels of DOPAC were increased by IBO in the striatum ($F_{2,17} = 39.11$, $p < 0.0001$) and hypothalamus ($F_{2,17} = 6.47$, $p < 0.01$), but not in the cortex. The IBO-induced elevation of DOPAC was significant only at the 100-mg/kg dose. HVA was increased in striatum ($F_{2,17} = 14.49$, $p < 0.001$) and hypothalamus ($F_{2,17} = 4.13$, $p < 0.05$), and these effects followed DOPAC changes.

The data in FIGURE 4 illustrate the effects of MK-801 on DA metabolism in the

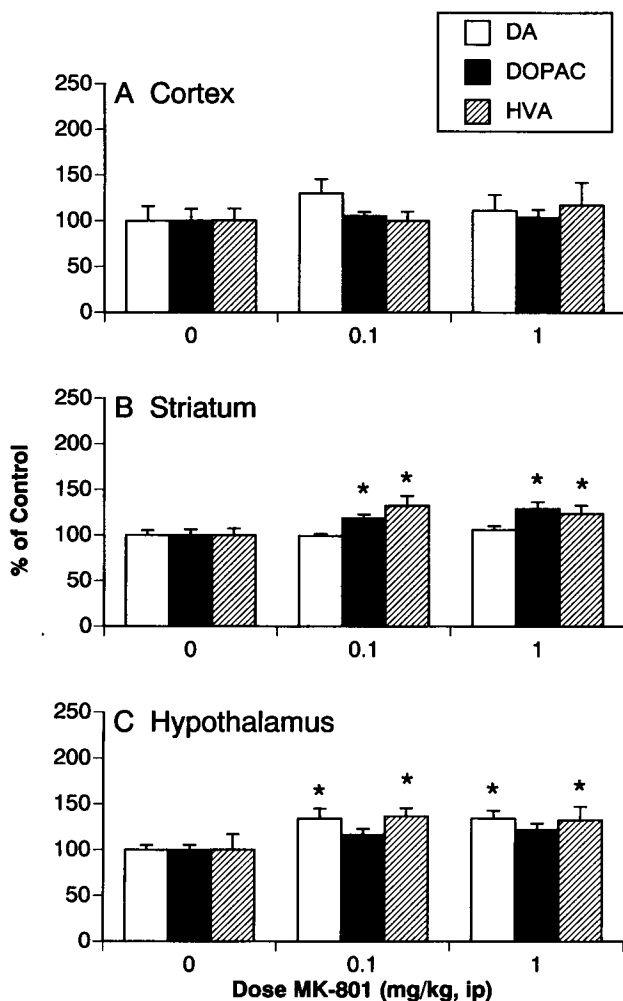


FIGURE 4. Effect of i.p. saline or MK-801 (0.1 & 1.0 mg/kg) on DA, DOPAC and HVA concentrations in the (A) frontal cortex, (B) striatum and (C) hypothalamus of male rats. Groups of rats ($n = 6-8$ rats/group) were sacrificed 30 min after MK-801 treatment. Values are expressed as % control of the data from saline-treated rats (control values shown in FIG. 3 legend). * $p < 0.05$ with respect to time zero control.

same three brain areas. MK-801 did not affect DA levels in the cortex or striatum; however, MK-801 increased DA levels in the hypothalamus ($F_{2,17} = 5.06$, $p < 0.05$) and this elevation was significant at the 0.1-mg/kg and 1.0-mg/kg doses. DOPAC levels were increased by MK-801 only in the striatum ($F_{2,17} = 7.06$, $p < 0.01$). HVA levels were elevated after MK-801 in the striatum ($F_{2,17} = 3.83$, $p < 0.05$) and hypothalamus ($F_{2,17} = 3.63$, $p < 0.05$), and this effect was significant at both doses of MK-801.

TABLE 2. summarizes the effects of IBO and MK-801 on plasma hormone levels. IBO elevated plasma prolactin ($F_{2,17} = 5.63$, $p < 0.01$) but MK-801 did not. Corticosterone secretion was stimulated by IBO ($F_{2,17} = 30.50$, $p < 0.0001$) and MK-801 ($F_{2,17} = 32.71$, $p < 0.0001$). The IBO-induced increase in corticosterone occurred at the 100-mg/kg dose of drug, whereas the MK-801-induced increase was apparent at both 0.1-mg/kg and 1.0-mg/kg doses.

DISCUSSION

In the present study, acute IBO administration produced a number of effects that included: (1) a decrease in brain tissue levels of DA, (2) a coincident increase in the DA metabolites DOPAC and HVA, and (3) an elevation of plasma prolactin and corticosterone. The IBO-induced changes in DA metabolism and neuroendocrine secretion reported here are in accordance with previous findings.^{27,28,32,33} Most importantly, the actions of MK-801 on these same neurobiological endpoints did not resemble the actions of IBO. For example, MK-801 failed to reduce tissue levels of DA in any brain region at any dose tested. While MK-801 was a potent stimulator of corticosterone secretion, this drug did not affect prolactin. The collective results indicate the effects of IBO on DA metabolism and prolactin secretion do not involve an MK-801-like action.

As mentioned in the introduction, mesolimbic DA neurons are known to play a critical role in the addictive properties of abused drugs.^{23,24} Therefore, it seems conceivable that antiaddictive properties of IBO might involve alterations in DA neurotransmission. We found that IBO caused a dramatic reduction in tissue levels of DA along with a rise in the levels of DOPAC and HVA. This profile of IBO effects was consistently observed in every brain region examined, and these results concur with previous studies performed in rats³² and mice.³³ Interestingly, acute IBO pretreatment (40 mg/kg, i.p., – 2 hr) attenuates the cocaine-induced elevation in extracellular DA and its associated locomotor stimulation.^{33,34} In conjunction with the present data, such results suggest that IBO may diminish the effects of cocaine via a reduction in synaptic DA availability. Al-

TABLE 2. Effects of IBO and MK-801 on Plasma Levels of Prolactin and Corticosterone in Rats

Treatment (ng/ml)	Prolactin (ng/ml)	Corticosterone
Saline, 1 ml/kg	9.6 ± 1.2	126.2 ± 21.2
IBO, 10 mg/kg	15.8 ± 2.4	100.0 ± 29.2
IBO, 100 mg/kg	26.3 ± 4.8*	383.5 ± 21.3*
MK-801, 0.1 mg/kg	11.7 ± 2.7	348.4 ± 39.7*
MK-801, 1.0 mg/kg	5.5 ± 0.8	487.9 ± 40.5*

Note: Rats were treated with i.p. saline, IBO (10 and 100 mg/kg) or MK-801 (0.1 and 1.0 mg/kg) and decapitated 30 min later. Plasma hormone levels are expressed as means ± SEM for $n = 6$ –8 rats/group.

* $p < 0.05$ compared to saline-injected control group.

ternately, the effects of IBO observed in the present study were transient (<2 hr) whereas some antiaddictive effects of the drug are long-lasting (>19 hr). Thus, our findings cannot account for the long-lasting actions of IBO.

MK-801 did not mimic the effects of IBO on DA metabolism. Tissue levels of DA were never decreased by MK-801, and this drug actually increased DA levels in the hypothalamus. Analogous to IBO, MK-801 did elevate DOPAC and HVA levels; however, the effects of MK-801 on DA metabolites were modest and region specific, in agreement with findings of others.^{30,35} The data indicate that the actions of IBO on acute DA transmission do not involve blockade of NMDA-coupled ion channels.

The mechanism whereby IBO affects DA function is unclear. While IBO does not display significant affinity for DA receptors,^{22,36} the drug does bind with 1.5–4.0 μM potency at DA transporters labeled by the cocaine congeners [³H]WIN-35,248 and [¹²⁵I]-RTI-121.^{14,33,37} In contrast, Broderick *et al.*³⁴ showed that IBO has >100 μM affinity for DA transporters labeled with the piperazine derivative [³H]GBR-12935. These results suggest that IBO displays different DA transporter binding affinities depending upon the radioligand used to label these sites. One explanation consistent with the data is that IBO recognizes different domains on the DA transporter protein, and this possibility merits further investigation.

In vivo microdialysis studies in rats demonstrate that IBO alters extracellular DA concentrations differentially depending upon brain region. When examined 1 hr after IBO injection (40 mg/kg, i.p.), dialysate DA is increased in the frontal cortex, decreased in striatum, and unaltered in the nucleus accumbens.³⁸ Using *in vivo* microvoltammetry methods, Broderick and co-workers³⁴ confirmed that IBO does not affect extracellular DA in the nucleus accumbens. The region-specific effects of IBO on extracellular DA are distinct from the uniform effects of the drug on postmortem indices of DA metabolism across brain areas. Taken together the data suggest that IBO interacts with DA transporter sites, but the effects of the drug on DA metabolism are not secondary to elevation of synaptic DA.

In a recent study, Staley and co-workers¹⁴ proposed that IBO might promote redistribution of intraneuronal DA from vesicular to cytoplasmic pools. While this 'redistribution' hypothesis is merely speculative, there is circumstantial evidence supporting the concept. For example, IBO displays low μM potency at vesicular monoamine transporters (VMAT) labeled with [¹²⁵I]tetraabenazine;¹⁴ these sites are crucial for the translocation of DA into synaptic vesicles. An IBO-induced effect on VMAT which disrupts compartmentalization of DA within vesicles could redistribute DA into the cytoplasm. Under such circumstances, rapid metabolism of transmitter by monoamine oxidase would account for the dramatic decrease in tissue DA content and the parallel increase in acid metabolites. Behavioral findings are consistent with the notion that IBO impairs vesicular storage of DA, at least transiently. Sershen and colleagues³³ showed that acute IBO pretreatment (40 mg/kg, i.p., —2 hr) blocks locomotor activity produced by cocaine, but not amphetamine, in mice. It is well established that cocaine-induced locomotor stimulant effects are dependent upon a reserpine-sensitive vesicular pool of DA, whereas the effects of amphetamine are not (reviewed in Ref. 39). Thus IBO, like reserpine, is able to distinguish between two type of stimulants: DA reuptake blockers (*i.e.*, cocaine) and DA releasers (*i.e.*, amphetamine). Clearly, more studies examining the effects of IBO on DA neuronal dynamics are warranted.

In the present work, IBO caused a transient increase in plasma prolactin and a prolonged rise in plasma corticosterone. MK-801 was a potent stimulator of corticosterone secretion but did not affect prolactin, confirming the findings of Pechnick and colleagues.⁴⁰ These data demonstrate that IBO-induced stimulation of corticosterone secretion, but not prolactin secretion, may involve an MK-801-like action. The mechanism(s) underlying the prolactin-releasing capability of IBO are not known. Prelimi-

nary data indicate this effect is centrally-mediated, since intraventricular administration of IBO (50–200 µg) increases circulating prolactin and corticosterone in rats (Baumann, unpublished). It would be logical to assume that DA is involved with the prolactin response to IBO, because hypothalamic DA exerts a predominant inhibitory influence on the secretion of this hormone. Thus if IBO decreases extracellular DA in the median eminence, as it does in the striatum, then prolactin secretion would be stimulated due to removal of DA inhibition. There is currently no direct evidence for, or against, this proposal.

It is noteworthy that the profile of hormone secretion produced by IBO resembles that of 5-HT-releasing agents such as fenfluramine.⁴¹ Several lines of evidence indicate that endocrine effects of IBO might be mediated via stimulation of 5-HT neurotransmission. IBO exhibits a 550-nM affinity for 5-HT transporters labeled by [¹²⁵I]RTI-55^{14,37} and IBO increases extracellular 5-HT in rat brain as assessed by *in vivo* methods.^{34,37} In rats trained to discriminate IBO (10 mg/kg, i.p.) from saline, fenfluramine partially generalizes to the IBO cue.²⁹ Finally, IBO elicits behaviors such as tremor and forepaw treading that are components of the 5-HT behavioral syndrome.^{5,10} Based on these observations, it is tempting to speculate that IBO increases prolactin and corticosterone secretion by a 5-HT mechanism. However, this hypothesis remains to be tested empirically.

In summary, IBO caused a spectrum of actions which included stimulation of central DA metabolism and elevation of stress axis hormones. MK-801 did not fully mimic the effects of IBO on these specific response variables. On the other hand, a preponderance of evidence suggests that IBO does mimic the effects of MK-801 in a variety of *in vitro* and *in vivo* bioassays.^{7,16,17} The explanation for this apparent paradox is most likely related to the fact that NMDA-coupled ion channels represent only one of multiple IBO targets in the brain. As pointed out by others, the nonselective nature of IBO could be the defining characteristic of the drug's therapeutic potential.^{14,22,37} Stated another way, the ability of IBO to simultaneously influence neural pathways involved with cognition (NMDA), mood (5-HT), and reward (DA), might underlie the unique antiaddictive effects of the drug. Future investigations should address the relative importance of specific IBO binding sites in mediating specific IBO actions. Hopefully, such studies will help to unravel the mysteries of this complex and ancient drug.

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